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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/606,804	06/28/2000	Amy S. Lee	06666-040001	5664

20985 7590 12/24/2003

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EXAMINER	
WHITEMAN, BRIAN A	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 12/24/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/606,804	LEE, AMY S.	
	Examiner	Art Unit	
	Brian Whiteman	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *3 October 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21,30-35 and 37-63* is/are pending in the application.

4a) Of the above claim(s) *10-14,17-21,44,47-62* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9,15,16,30-35,37-43,45,46 and 63* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *10/3/03* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Final Rejection

Claims 1-21, 30-35, and 37-63 are pending.

Applicants' traversal, the amendment to claims 1–9, 15, 16, 30, 31, 37-39, 43 and 45, the cancellation of claims 22-29 and 36, the addition of claim 63 is acknowledged and considered filed on 10/3/03.

Election/Restrictions

Claims 10-14, 17-21, 44, and 47-62 stand withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 10 filed on 11/7/02.

Priority

Applicant's arguments (see pages 13-14) filed 10/3/03 have been fully considered but they are not persuasive. See the reasons in paper no. filed on 5/1/03.

With respect to applicants' argument that, "Applicants submit that the written disclosure of the priority document is supplemented by the knowledge held by one of ordinary skill in the art (page 14)" and "It is well settled law that an Applicant need not include disclosure that was well known in the art" and "It was well within the capabilities of the skilled artisan, at the time the priority document was filed, to take such teachings and modify the protocol," the argument is not found persuasive because the journal article does not provide sufficient description, sufficient

guidance and/or factual evidence under 112 first paragraph for treating a genus of cell proliferative disorders embraced by the claims. Given the relatively incomplete understanding in the biotechnological field involved, e.g., gene therapy, and the lack of a reasonable correlation between the narrow disclosure in the journal article and the broad scope of protection sought in the claims, the non-provisional application does not enjoy priority to the provisional application. See MPEP 2164.08.

With respect to applicant's argument that, "It was well within the capabilities of the skilled artisan, at the time the priority document was filed, to take such teachings and modify the protocol," the argument is not found persuasive because "It is not sufficient for purposes or the written description requirement of Section 112 that the disclosure, when combined with the knowledge in the art, would lead one to speculate as to modifications that the inventor might have envisioned, but failed to disclose." *Lockwood v. American Airlines, Inc.,* 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997). See MPEP 2163.

Furthermore, the court in Enzo 188 F.3d at 1374, 52 USPQ2d at 1138 states:

> It is well settled that patent applications are not required to disclose every species encompassed by their claims, even in an unpredictable art. However, there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the invention as broadly as it is claimed.
> In re Vaeck, 947 F.2d 48, 496 & n.23. 30 USPQ2d 1438, 1445 &n23 (Fed. Cir. 1991)(citation omitted). Here, however, the teachings set forth in the specification provide no more than a "plan" or "invitation" for those of skill in the art to experiment...; they do not provide sufficient guidance or specificity as to how to execute that plan. See Fiers v. Revel. 984 F.2d.1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993); In re Wright, 999 F.2d...[1557], 1562, 27 USPQ2d...[1510], 1514. [Footnote omitted].

On this record, it is apparent that the provisional application provides no more than a plan or invitation for experimentation in view of the art of record exemplifying the unpredictability of gene therapy to use the claimed method.

See also Genetech Inc. v. Novo Nordisk A/S, 108 F.3d 1361, 1366, 42, USPQ2d 1001, 1005 (Fed. Cir. 1997)

> ("Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable the public to understand and carry out the invention.")

In view of the state of the art for gene therapy at the time the application was filed and the lack of guidance provided by the journal article; the provisional does not provide reasonable detail for what protocols are required for different methods of gene therapy, and it would take one skilled in the art an undue amount of experimentation to reasonably extrapolate from the assertion in the argument to the full support of the claimed invention in the non-provisional application.

Drawings

The drawings were received on 10/3/03. These drawings are accepted.

The petition for color drawings filed on 6/28/00 has been GRANTED.

12/18/03

Claim Objections

Claim 3 is objected to because of the following informalities: the language of claim 3 is grammatically incorrect. Suggest inserting -- a -- before the term "rat" and "human" on line 2. Appropriate correction is required.

Applicant is advised that should claim 6 be found allowable, claim 63 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application

are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Response to Arguments

Applicant's arguments, see, filed on 10/3/03, with respect to 112 first paragraph written description rejection have been fully considered and are persuasive. The rejection of claims 1-9, 15, 16, 22-24, 26-43, and 45-46 has been withdrawn because of the amendment to the claims and cancellation of claims 22-24, 26-29 and 36. See pages 14-15.

Applicant's arguments, see, filed on 10/3/03, with respect to 112 second paragraph rejection have been fully considered and are persuasive. The rejection of claims 2, 3, 23, 36-43, 45 and 46 has been withdrawn because of the amendment to the claims and cancellation of claims 23 and 36. See pages 22-23.

Applicant's arguments, see, filed on 10/3/03, with respect to 102(a) rejection have been fully considered and are persuasive. The rejection of claims 1, 2, 4-9, 15, 16, 22, 23, 24, 26-29, 31, 35-40, 42 and 43 has been withdrawn because of the Declaration of Amy Lee filed under 1.132. See page 23.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 37-43, 45, and 46 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of reducing a cell proliferative disorder associated with glucose starvation in a subject comprising directly delivering a recombinant retroviral vector comprising a nucleic acid construct comprising a functional promoter comprising at least one stress-responsive non-coding regulatory sequence comprising at least two endoplasmic reticulum stress elements (ERSE) as set forth in SEQ ID NO: 1 from a rat grp78 coding sequence to a target cell, does not reasonably provide enablement for treating all cell proliferative disorders in a subject using all routes of administration. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

> Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in In re Wands, 858 F.2d 731, 8USPQ2d 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The invention is directed to producing a recombinant retroviral vector comprising a nucleic acid construct comprising at least one glucose responsive protein 78 non-coding regulatory sequence comprising at least two ERSE as set forth in SEQ ID NO: 1 and a heterologous nucleic acid sequence operatively linked to the regulatory sequence and using the construct in a method of treating a cell proliferative disorder in a subject.

Furthermore, and with respect to claim 37-43 and 45-46 directed to any vector useful for gene therapy and directed to treating a cell proliferative disorder in a subject; the state of the art

exemplified by Anderson et al., *Nature*, Vol. 392, pp. 25-30, April 1998, displays major consideration for any gene transfer or any DNA therapy protocol involve issues that include:

1) The type of vector and amount of DNA constructs to be administered,

2) The route and time course of administration, the sites of administration, and successful uptake of the claimed DNA at the target site;

3) The trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA product, the amount and stability of the protein produced, and

4) What amount of the expressed proteins considered to be therapeutically effective for a DNA therapy method.

In addition, all of these issues differ dramatically based on the specific vector used, the route of administration, the animal being treated, therapeutically effective amount of the DNA, and the disease being treated.

Anderson teaches that gene therapy is a powerful new technology that still requires several years before it will make a noticeable impact on the treatment of disease, and that several major deficiencies still exist including poor delivery systems, both viral and non-viral, and poor gene expression after genes are delivered (pp. 25-30).

Anderson further teaches that the reason for the low efficiency of gene transfer and expression in human patients is that we still lack the basis understanding of how vectors should be constructed what regulatory sequences are appropriated for which cell types (page 30, column 1, last paragraph). Furthermore, Verma, *Nature*, Vol. 389, pages 239-242, 1997, indicates that factors including the nature of the diseases and/or disorders, the nature of a DNA and/or target

tissue, and a delivery system and/or amounts of the DNA complexes employed in the delivery system that would generate a therapeutic effect *in vivo* must be considered for any gene therapy method to be successful (page 238, columns 1 and 2).

In further view of the doubts expressed above by Anderson and Verma, the state of the art at the time the application was filed and currently for cancer gene therapy as discussed by Vile et al., (*Gene Therapy*, Vol. 7, pp. 2-8, 2000). Vile teaches:

> The problems which gene therapy for cancer will take into the next millennium focus far less on the choice of therapeutic gene(s) to be used than on the means of delivering them. There is already a battery of genes that we know are very effective in killing cells, if they can be expressed at the right site and at appropriate levels. Nonetheless, until the perfect vector is developed, the choice of gene will remain crucially important in order to compensate for the deficiencies of the vectors we currently have available (page 2, 1st paragraph, left column). Whatever its mechanism, no single genes can be a serious contender unless it has a demonstrable bystander effect (page 2, right column). The requirement for such a bystander effect stems directly from the poor delivery efficiency provided by current vectors (page 2, right column).
>
> A genuine ability to target delivery systems to tumor cells distributed widely throughout the body of a patient would simultaneously increase real titers and efficacy. In truth, no such systemically targeted vectors exist yet. Injection of vectors into the bloodstream for the treatment of cancer requires not only that the vectors be targeted (to infect only tumor cells) but also that they by protected (from degradation, sequestration or immune attack) for long periods of time so that they can reach the appropriate sites for infection. Moreover, having reached such sites, the vectors must be able to penetrate into the tumor from the bloodstream before carrying out their targeted infection (page 4, bottom left column and top right column).
>
> Even the highest titer system is clearly not high enough yet to cure even local tumors. Therefore, there is a clear need to explore and exploit, a range of alternative options. The development of replication vectors for cancer gene therapy is the inevitable consequence of data from the early clinical trials. So far, a substantial therapeutic gap still exists between the overlap of the efficacy provided by, on the other hand, the potency of the therapeutic gene(s) and on the other, the efficiency of gene delivery provided by the vector. Only when these two 'therapeutic domains' approach each other will clinical efficacy result.

In view of the art of record at the time the application was filed, gene therapy was considered unpredictable.

The specification provides sufficient guidance for making a vector comprising a nucleic acid construct comprising a grp78 promoter sequence or a truncated rat grp78 promoter sequence and using the vector in a method of reducing a cell proliferative disorder associated with glucose starvation in a subject comprising directly administering the vector to cells involved in the proliferative disorder. However, the breadth of term "treating" embraces curing and preventing (see page 46) and in view of the In Re Wands Factors the full breadth of the term is not considered enabled. There are several problems with gene therapy and the specification does not provide sufficient guidance for how to overcome these problems, including the transient nature of gene therapy or what cells need to be targeted in order to prevent a cell proliferative disorder in a subject. In addition, the specification and art of record teach that the grp78 promoter is the major stress-inducible protein in cells having glucose starvation (IDS, Gazit et al. Cancer Research, Vol. 59:3100-3106, 1999). The disclosure does not provide sufficient guidance for how to use the claimed vector to treat cells that are not undergoing glucose starvation (e.g. slow growing tumors have a sufficient blood supply and do not experience glucose starvation). The state of the art cites that, "the spontaneous behavior of human tumors is somewhat different for that of malignant cells *in vitro*, and from that of experimental tumors in animal models" (Gomez-Navarro et al., *European Journal of Cancer*, Vol. 35, pp. 868, Table 1, 1999). Even if a therapeutic response using an *ex vivo* method of gene therapy for cancer in an experimental murine model using transfected cancer cells has been shown in the as-filed specification, it is not apparent as to how it is reasonably extrapolated to the full scope of the claimed invention,

encompassing treating all cell proliferative disorder in a subject. Thus, the full scope of the claimed methods is not considered enabled.

Furthermore, claims 37-43 and 45-46 read on using all routes of administration and claim 43 is directed to systemic administration to target cells involved in a proliferative disorder in a subject. It would take one skilled in the art an undue amount of experimentation to determine what route of administration (*e.g.* intravenous, dermal, nasal, rectal, vaginal, inhalation, or topical administration) other than direct administration would result in a therapeutic response using the claimed vector. The specification administers cancer cells transfected with retroviral vectors comprising a truncated grp 78 promoter operatively linked to a heterologous nucleic acid sequence to the shoulder of mice (page 72). The state of the art for the route of administration for gene therapy as exemplified by Verma, *Nature*, Vol. 389, pages 239-242, 1997, indicates that factors including the nature of the diseases and/or disorders, the nature of a DNA and/or target tissue, and a delivery system and/or amounts of the DNA complexes employed in the delivery system that would generate a therapeutic effect *in vivo* must be considered for any gene therapy method to be successful (page 238, columns 1 and 2). In addition, Vile teaches that there are no known vectors that can be used for systemically treating cancer in a subject (page 4). In view of the art of record and the lack of guidance provided by the specification for using all routes of delivery other than direct administration, it is not apparent to one skilled in the art how to reasonably extrapolate from direct administration to any other route of administration to generate a therapeutic response in reducing a proliferative disorder in a subject.

As a result, it is not apparent how one skilled in the art determines, without undue experimentation, which of the claimed recombinant retroviral vector generate a therapeutic effect

(curing or preventing), how is it apparent as to how one skilled in the art, without any undue experimentation, practices any nucleic acid therapy method as contemplated by the claims, particularly given the unpredictability of nucleic acid therapy as a whole and/or the doubts expressed in the art of record.

In conclusion, the as-filed specification and claims coupled with the art of record only provide sufficient guidance and/or evidence to reasonably enabled for using the claimed vector in a method of treating a cell proliferative disorder associated with glucose starvation in a subject comprising directly administering the vector to cells involved in the proliferative disorder. Given that gene therapy wherein any carrier is employed to correct a disease or a medical condition (e.g., cell proliferative disorder) in any subject was unpredictable at the time the invention was made, and given the lack of sufficient guidance as to a gene therapy effect produced by any gene delivery vector cited in the claims, one skilled in the art would have to engage in a large quantity of experimentation in order to practice the claimed invention based on the applicant's disclosure and the unpredictability of gene therapy.

Applicant's arguments filed 10/3/03 have been fully considered but they are not persuasive because in view of the In Re Wands Factor, the as-filed specification fails to provide sufficient guidance or evidence for one skilled in the art to practice the full scope of the claimed invention.

With respect to applicant's argument that, "Applicants submit that the claimed methods are clearly enabled for the treatment of a cell proliferative disorder associated with glucose starvation in a subject (page19)," the argument is not found persuasive because the breadth of term "treating" encompasses curing and preventing (see page 46) and in view of the In Re

Wands Factors the full breadth of the term is not considered enabled. In addition, the specification lacks sufficient guidance or evidence for one skilled in the art to use a therapeutic compound that inhibits cell proliferation associated with glucose starvation thereby treating the cell proliferative disorder to treating any cell proliferative disorder other than a cell proliferative disorder associated with glucose starvation. The specification fails to provide sufficient guidance one skilled in the art how to cure or prevent a cell proliferative disorder. The specification and the art of record lack, at the time the application was filed, lack sufficient guidance or evidence for one skilled in the art to reasonably correlate reducing a cell proliferative disorder in a mouse using ex vivo gene therapy method to curing or preventing a cell proliferative disorder in a subject. The art of record is absent for curing or preventing a cell proliferative disorder in a subject.

With respect to applicant's argument that, "Applicant notes that the in vitro and in vivo studies provided in the specification confirm that the grp78 promoter is capable of inducing high levels of HSVtk expression in the tumor environment, leading to complete eradication of sizable tumors in their syngeneic host after GCV treatment (see pages 20-21)," the argument is not found persuasive for the reasons set forth above and because the specification fails to provide sufficient guidance how to reasonably correlate ex vivo gene therapy to the full scope of the claimed methods in view of the problems of course of delivering the vector (See Vile, supra and Verma, supra). More specifically, Vile teaches that there are no known vectors that can be used for systemically treating cancer in a subject (page 4). The specification fails to provide sufficient guidance or evidence to use all routes of administration other than direct administration to reduce

cell proliferative disorder associated with glucose starvation can be used without an undue amount of experimentation.

In response to applicant's argument that, "One of ordinary skill in the art would expect that the successful in vitro and in vivo experiments described in the present application would show that the vectors would have a therapeutic effect when administered to a human patient, i.e., that there would be a reasonable correlation between the in vitro and in vivo data and clinical human effectiveness (page 20)". The argument is not found persuasive because MPEP § 716.01(c) states:

> The arguments of counsel cannot take the place of evidence in the record. In re Schulze,346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965). Examples of attorney statements which are not evidence and which must be supported by an appropriate affidavit or declaration include statements regarding unexpected results, commercial success, solution of a long-felt need, inoperability of the prior art, invention before the date of the reference, and allegations that the author(s) of the prior art derived the disclosed subject matter from the applicant.

This is case here. Other than the assertion, the applicant provides no guidance and/or evidence to support the assertion.

With respect to applicant's argument that, "The office action appears to suggest that, absent actual clinical data supporting the efficacy of a claimed gene therapy related treatment" and "the law is clear that when those having skill in this art are fully able to utilize claimed subject matter as described in the specification, clinical testing should not be made a prerequisite to patentability" and "First, it is not necessary to describe and prove actual results of every

possible manipulation, combination or variation of vectors of interest and animal species in order to establish enablement of an invention." See pages 20-22. The argument is not found persuasive because the examiner is not asking for clinical data to support the full scope of the claimed invention. The examiner applied the In Re Wands Factors, and determined (see reasons set forth above under 112 first paragraph enablement) that the as-filed specification is not enabled for the full scope of the claimed invention. The specification fails to provide sufficient guidance or evidence to use all routes of administration other than direct administration to reduce cell proliferative disorder associated with glucose starvation can be used without an undue amount of experimentation. The specification and the art of record lack, at the time the application was filed, lack sufficient guidance or evidence for one skilled in the art to reasonably correlate reducing a cell proliferative disorder in a mouse using ex vivo gene therapy method to curing or preventing a cell proliferative disorder in a subject. The art of record is absent for curing or preventing a cell proliferative disorder in a subject.

Furthermore, with respect to the assertion, "it is not necessary to describe and prove actual results of every possible manipulation, combination or variation of vectors of interest and animal species in order to establish enablement of an invention."

The court in Enzo 188 F.3d at 1374, 52 USPQ2d at 1138 states:

> It is well settled that patent applications are not required to disclose every species encompassed by their claims, even in an unpredictable art. However, there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the invention as broadly as it is claimed.
> In re Vaeck, 947 F.2d 48, 496 & n.23. 30 USPQ2d 1438, 1445 &n23 (Fed. Cir. 1991)(citation omitted). Here, however, the teachings set forth in the specification provide no more than a "plan" or "invitation" for those of skill in the art to experiment...; they do not provide sufficient guidance or specificity as to how to execute that plan. See Fiers v. Revel. 984 F.2d.1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993); In re Wright, 999 F.2d...[1557], 1562, 27 USPQ2d...[1510], 1514. [Footnote omitted].

On this record, it is apparent that the specification provides no more than a plan or invitation for experimentation in view of the breadth of the term "treating" provided by the specification, lack of guidance for using all routes of administrations to treat a cancer proliferative disorder in a subject, and in view art of record exemplifying the unpredictability of using gene therapy to prevent or cure a cell proliferative disorder in a subject, for those skilled in the art to experiment with level of expression so as to provide a therapeutic method of gene therapy as intended by the as-filed specification at the time the invention was made.

See also Genetech Inc. v. Novo Nordisk A/S, 108 F.3d 1361, 1366, 42, USPQ2d 1001, 1005 (Fed. Cir. 1997)

> ("Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable the public to understand and carry out the invention.")

In view of the art of record and the lack of guidance provided by the specification; the specification does not provide reasonable detail for what protocols are required for preventing or treating a cell proliferative disorder in a subject, and it would take one skilled in the art an undue amount of experimentation to reasonably extrapolate from the guidance in the specification to the full breadth of the claimed invention. Therefore, the as-filed specification is not enabled for the full scope of the claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 37-43, 45 and 46 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 37-43, 45 and 46 recite the limitation "claim 64". There is insufficient antecedent basis for this limitation in the claims because there is no claim 64.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or non-obviousness.

Claims 1, 2, 4-9, 15, 16, 31-35, 37-43, 45, 46 and 63 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gazit et al. (IDS, Cancer Research, 55:1660-1663, 1995) taken with Walther et al. (IDS, Molecular Biotechnology, 6:267-286, 1996) in further view of Mullen (IDS, Pharmac. Ther. 63:199-207, 1994). Gazit teaches that a 600-base pair subfragment of grp78 promoter used as an internal promoter within a retroviral vector is able to confer high level of

expression of a reporter gene in a murine fibrosarcoma *in vivo* (page 1663). Gazit teaches that since most anticancer agents are extremely toxic when expressed at high levels in normal cells, the discovery of grp78 with stringently enhanced expression in a tumor environment could be useful in cancer gene therapy. However, Gazit does not specifically teach a vector comprising a grp promoter operatively linked to a heterologous sequence encoding an enzyme and using the vector in a method of pro-drug cancer gene therapy in an animal.

However, at the time the invention was made, cancer pro-drug gene therapy was well known to one ordinary skill in the art. Walther et al. reviews methodologies for targeted vectors used in cancer gene therapy and teaches the advantaged of vectors comprising a therapeutic gene operably linked to the grp78 promoter (page 280-281). In addition, Mullen teaches delivery of suicide genes *in vivo* using a viral vector (page 202-203).

At the time the invention was made it would have been *prima facie* obvious for a person of ordinary skill to make a vector comprising a nucleic acid encoding an enzyme that converts a non-therapeutically effective compound to a therapeutically effective compound operatively linked to the grp78 promoter. One of ordinary skill in the art would have been motivated to make the vector because Gazit and Walther teach the advantages of using the grp78 promoter in a vector for cancer gene therapy.

In addition, at the time the invention was made it would have been *prima facie* obvious for a person of ordinary skill to use the claimed vector in a method of prodrug cancer gene therapy. One of ordinary skill in the art would have been motivated to use the vector because the grp78 promoter confers high level of expression of a gene in a murine fibrosarcoma *in vivo*.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Applicant's arguments filed 10/3/03 have been fully considered but they are not persuasive because argument is based on the Declaration of Amy Lee filed under 1.132.

The Declaration of Amy Lee under 37 CFR 1.132 filed 10/3/03 is insufficient to overcome the rejection of claims 1, 2, 4-9, 15, 16, 31-35, 37-43, 45, 46 and 63 over the 103(a) rejection as set forth above because: the article (Gazit et al., Cancer Research, 55:1660-1663, 1995) used in the rejection is not discussed in the Declaration. Furthermore, even if the article was discussed in the Declaration and Amy Lee provides sufficient guidance that all of the authors were under her supervision, the Declaration would not have been found persuasive because the Gazit article has a 102(b) date and a Declaration under 1.132 cannot be used to overcome the rejection. See MPEP 2133.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37

CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Whiteman whose telephone number is (703) 305-0775. The examiner can normally be reached on Monday through Friday from 7:00 to 4:00 (Eastern Standard Time), with alternating Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang, acting SPE - Art Unit 1635, can be reached at (703) 306-3217.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Brian Whiteman
Patent Examiner, Group 1635

Scott D. Priebe

SCOTT D. PRIEBE, PH.D
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Applicant	:	Lee
Serial Number	:	09/606,804
Filing Date	:	06/28/2000
Art Unit	:	1635

Applicant's petition under 37 CFR 1.84(a)(2), filed 6/28/2000, for color drawings has been approved and entered.

ANDREW WANG
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600